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REVIEW

Bone mineral density in childhood cancer survivors during and after oncological treatment: A systematic review and meta-analysis

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Abstract

Osteoporosis poses a significant concern for childhood cancer survivors (CCS). While recommendations for surveillance and management of bone mineral density (BMD) exist, no systematic review and meta-analysis has been undertaken to quantify BMD Z-scores in childhood cancer patients undergoing cancer treatment and survivors who have completed treatments. Accordingly, we conducted a systematic review with a 3-level mixed-effects meta-analysis to examine the course of BMD Z-scores in childhood cancer patients and survivors and identified possible moderators using meta-regression models. A systematic search was conducted in CINAHL, Embase, PubMed, SPORTDiscus, and Web of Science databases from inception to November 2023. We included studies that involved children and adolescents diagnosed with cancer before the age of 18 who were undergoing cancer treatment or had completed treatments and reported lumbar spine, hip/femoral neck, or total body BMD Z-scores derived from dual-energy x-ray absorptiometry. Forty-nine studies (4547 participants) were included in the meta-analysis. BMD Z-scores across different sites decreased with respect to baseline in children undergoing cancer treatment (mean difference: − 0.36, 95% CI − 0.62 to − 0.11; $p = .01$) and remained low following treatment in child and adolescent CCS (lumbar spine: − 0.85 SD, 95% CI − 1.17 to − 0.54; $p < .001$; hip/femoral neck: − 1.03 SD, 95% CI − 1.38 to − 0.68; $p < .001$), and adult CCS (lumbar spine: − 0.46 SD, 95% CI − 0.67 to − 0.26; $p < .001$; hip/femoral neck: − 0.36 SD, 95% CI − 0.57 to − 0.16; $p < .001$). Hip/femoral neck BMD Z-scores were moderated by age at assessment ($p = .006$), time from diagnosis ($p = .004$), sex ($p = .037$), and height ($p = .026$). Lumbar spine BMD Z-scores were moderated by age at assessment ($p = .018$), and sex ($p = .015$). In conclusion, childhood cancer patients and survivors experience reductions in BMD. Future research should evaluate the implications of regular physical activity, targeted exercise medicine, and nutrition therapy as first-line countermeasures to mitigate the declines in bone health.

Keywords Bone mineral density · Childhood cancer · Dual-energy x-ray absorptiometry

Introduction

Advancements in the treatment of childhood cancers have increased the 5-year survival rate to over 85% [1]. While this progress is a remarkable milestone, it has also revealed the long-term sequelae associated with cancer and its treatment. Osteoporosis poses a significant concern for childhood cancer survivors (CCS), with numerous studies indicating an elevated risk of bone fragility fractures and reductions in bone mineral density (BMD) measured using dual-energy x-ray absorptiometry (DXA) [2, 3].

In a previous meta-analysis by Morales and colleagues [4], the authors found no significant difference in DXA-derived BMD (g/cm^2) between CCS compared with healthy

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counterparts. Their analysis, however, was restricted to only total body BMD and was limited by the small number of included studies ($n = 4$). Evaluating BMD at clinically relevant sites, such as the spine and the hip, in individuals predisposed to BMD deficits and fragility fractures (particularly vertebral) is crucial [5]. Furthermore, pediatric, and adult normative databases are available to convert raw BMD scores to sex- and age-specific Z-scores. This standardized score allows for the aggregation and comparison of data from multiple studies, enhancing the statistical power of the meta-analysis. Definitions of osteopenia/osteoporosis are also heavily dependent on and delineated by BMD Z-scores [6, 7]. Thus, evaluating DXA-derived BMD Z-scores and trajectories on serial measurements can provide clinicians with better insights and enhance surveillance strategies [8].

Although researchers have provided recommendations for counselling [9] and management [3] of BMD deficits for CCS, to our knowledge, no systematic review and meta-analysis has been undertaken to quantify BMD Z-scores in childhood cancer patients undergoing cancer treatment and CCS who have completed treatment. Accordingly, the purpose of this study was to systematically review and analyse lumbar spine, hip/femoral neck, and total body BMD Z-scores in childhood cancer patients and CCS and to examine whether pre-defined clinical characteristics were associated with BMD Z-scores.

Materials and methods

A meta-analysis was undertaken to investigate BMD Z-scores in childhood cancer patients and survivors. Additionally, meta-regression models were used to examine moderators of BMD Z-scores. All procedures undertaken in this study were reported in accordance with the Cochrane Back Review Group (CBRG) [10], the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11, 12], and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [13]. A detailed description of the search strategy is available in the Supplementary information (Appendix).

Search strategy and study selection procedure

This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD42023466971. A systematic search was conducted using CINAHL, Embase, PubMed, SPORTDiscus, and Web of Science databases from inception to November 2023. The search strategy was undertaken with the assistance of a librarian, using controlled vocabulary and free-text terms (Supplementary information Appendix). In addition to database searching, a manual search of references was performed to detect potentially eligible articles for inclusion. Titles and abstracts were independently evaluated by two authors (A.M.M. and F.B.) following the eligibility criteria. Abstracts were selected for full-text evaluation when they did not provide sufficient information. Full-text articles meeting the criteria were retrieved and read independently by both reviewers (A.M.M. and F.B.) and assessed for inclusion in the study. Disagreements regarding the final list of studies to include were resolved by consensus.

To evaluate whether cancer treatments affect BMD, we included studies that: (a) involved children and adolescents diagnosed with cancer before the age of 18 and undergoing cancer treatments; (b) reported lumbar, hip/femoral neck or total body DXA BMD Z-scores; and (c) were of prospective, longitudinal design or interventional-based with a usual-care control group.

To evaluate whether BMD in CCS differs from children who have not had cancer, we included studies that: (a) involved children and adolescents diagnosed with cancer before the age of 18 who had completed treatments. There were no restrictions on the age at BMD assessment; however, studies were only included if the cohort was composed exclusively of CCS under or above 18 years old. Thus, studies with a cohort consisting of a mixed-aged group of children, adolescents, and adults were ineligible; and (b) reported lumbar, hip/femoral neck or total body DXA BMD Z-scores, irrespective of the study design.

Exclusion criteria were: (a) patients/survivors with osteonecrosis; however, when studies provided subgroups of patients with and without osteonecrosis, the group without osteonecrosis was included in the analysis; (b) not reporting outcomes included in this review; (c) studies written in a language other than English; and (d) case reports/series, editorials, abstracts, commentaries, and reviews.

Data extraction

Data extraction was performed by two authors (A.M.M. and H.L.) using a structured form in Covidence, and inconsistencies were resolved during weekly meetings. Study information, including sample size, cohort year, study design, type of cancer diagnosis, age at cancer diagnosis, age at BMD assessment, race and ethnicity, fracture details, DXA manufacturer, model, software, and reference used, were extracted along with the outcomes of interest. The primary outcome was BMD Z-score. We also took the opportunity to examine fracture prevalence based on the available data from the included studies. Data for the primary endpoint was extracted as mean and standard deviation (SD) or in a manner allowing transformation into mean and SD. In studies where medians, ranges, or interquartile ranges were provided instead of the mean and SD [14–24], these were estimated using the formula from Wan et al. [25]. When the standard error (SE) was reported instead of SD [26–30], the latter was obtained using the formula from Altman and Bland [31]. As

for studies that followed a normal distribution and provided the mean and confidence interval [30, 32], we transformed the confidence interval into SE and then calculated the SD [31] according to Cochrane recommendations [33]. Finally, when graphs were presented instead of numerical data [27, 34–39], data were extracted from the plots using a specific tool for data extraction (WebPlotDigitizer, San Francisco, CA, USA) [36–40].

For the studies in children undergoing treatments, baseline (at diagnosis) and time point closest to 12 months (first year from diagnosis), 24 months (second year from diagnosis), or 36 months (3 years from diagnosis) were extracted, and the mean difference between the baseline and the second time point was calculated. For the interventional trials that were included in the longitudinal analysis [36, 41, 42], only data from the control group were extracted.

Risk-of-bias assessment

The methodological quality of the included studies was assessed independently in Covidence by two authors (A.M.M. and H.L.) using the Newcastle–Ottawa Scale (NOS). The score ranges from 0 to 9 with higher scores indicating higher quality (0–3 points low quality, 4–6 points moderate quality, 7–9 points high quality).

Statistical analysis

A three-level mixed-effects meta-analysis with study included as a random effect was performed to examine BMD Z-scores in children undergoing cancer treatment and CCS. The Z-score represents the relative strength and direction of BMD compared with age- and sex-matched normative data. Thus, a negative effect size would reflect lower BMD than the average population. Cluster robust point estimates and 95% CI are reported, weighted by inverse sampling variance to account for the within- and between-study variance (tau^2). Additionally, restricted maximal-likelihood estimation was used in all models. Statistical significance was assumed when the mean difference (MD) was below an alpha level of $p < 0.05$. Statistical heterogeneity was assessed using the Cochran Q test, with I^2 greater than 50% indicating high heterogeneity. Publication bias was explored using contour-enhanced funnel plots and Egger's test [43]. Heterogeneity, publication bias, sensitivity, and moderator analyses were performed to substantiate the results. For fracture prevalence, a random effects model with double-arcsine transformation was used [44].

Subgroup analyses for longitudinal studies were conducted for: (a) time from diagnosis, and (b) BMD region. Multilevel models with robust estimates were generated for each subgroup, and fixed effects with the moderator's model were used for comparison. Meta-regression models were undertaken to test the association between potential moderators and outcomes of interest. Hypothesized moderators of BMD included age at diagnosis, age at assessment, time from diagnosis, sex, cohort year, and height. Statistical significance was assumed when $\beta \pm SE$ was below an alpha level of $p < 0.05$. Analyses were conducted using the meta [45], metafor [46] and clubSandwich [47] packages in R (R Core Team, version 4.3.3., 2024).

Results

A total of 9381 studies were retrieved from our search. After removing duplicates, 7885 potential records were identified for title and abstract screening. Of these, 7090 records were excluded due to irrelevance to the research question. Further 746 reports were then excluded for specific reasons described in Fig. 1. Therefore, 49 articles [14–24, 26–30, 32, 34–39, 41, 42, 48–71] were included in the present meta-analysis.

Study characteristics

A general description of the characteristics of each of the 49 studies (4547 participants) is shown in the Supplementary information (Tables 2, 3, 4). The study distribution was as follows: 14 studies included children newly diagnosed with cancer and undergoing treatment (1581 participants; mean age [SD] 8 [1.6] years) [21–23, 32, 35–39, 41, 42, 48–50], 18 studies included CCS below the age of 18 who had completed treatments (1094 participants; mean age [SD] 12 [1.7] years) [14–16, 24, 28–30, 34, 51–60], 16 studies included CCS above the age of 18 who had completed treatments (1777 participants; mean age [SD] 26.6 [4.0] years) [17–20, 26, 27, 61, 62, 64–71], and one study (95 participants) [63] included separate analysis for both age groups. NOS risk-of-bias assessments are presented in the Supplementary information (Tables 5, 6, 7).

BMD Z-scores in children undergoing treatment

Twenty-eight effect sizes across 14 studies were included in the main model for lumbar spine, hip/femoral neck, or total body BMD Z-scores. BMD Z-score significantly decreased from baseline (at diagnosis) in children undergoing cancer treatment (Mean difference: −0.36, 95% CI −0.62 to −0.11; $p = 0.01$; Supplementary Fig. 1). Heterogeneity (I^2) was 73%, and the contour-enhanced funnel plot indicated the presence of publication bias ($\tau = 2.2$; $p = 0.039$; Supplementary Fig. 2). Overall and subgroup analyses are presented in Table 1. While the duration from diagnosis was not associated with differences in BMD Z-score ($p = 0.816$), BMD site was a significant moderator ($p < 0.001$).

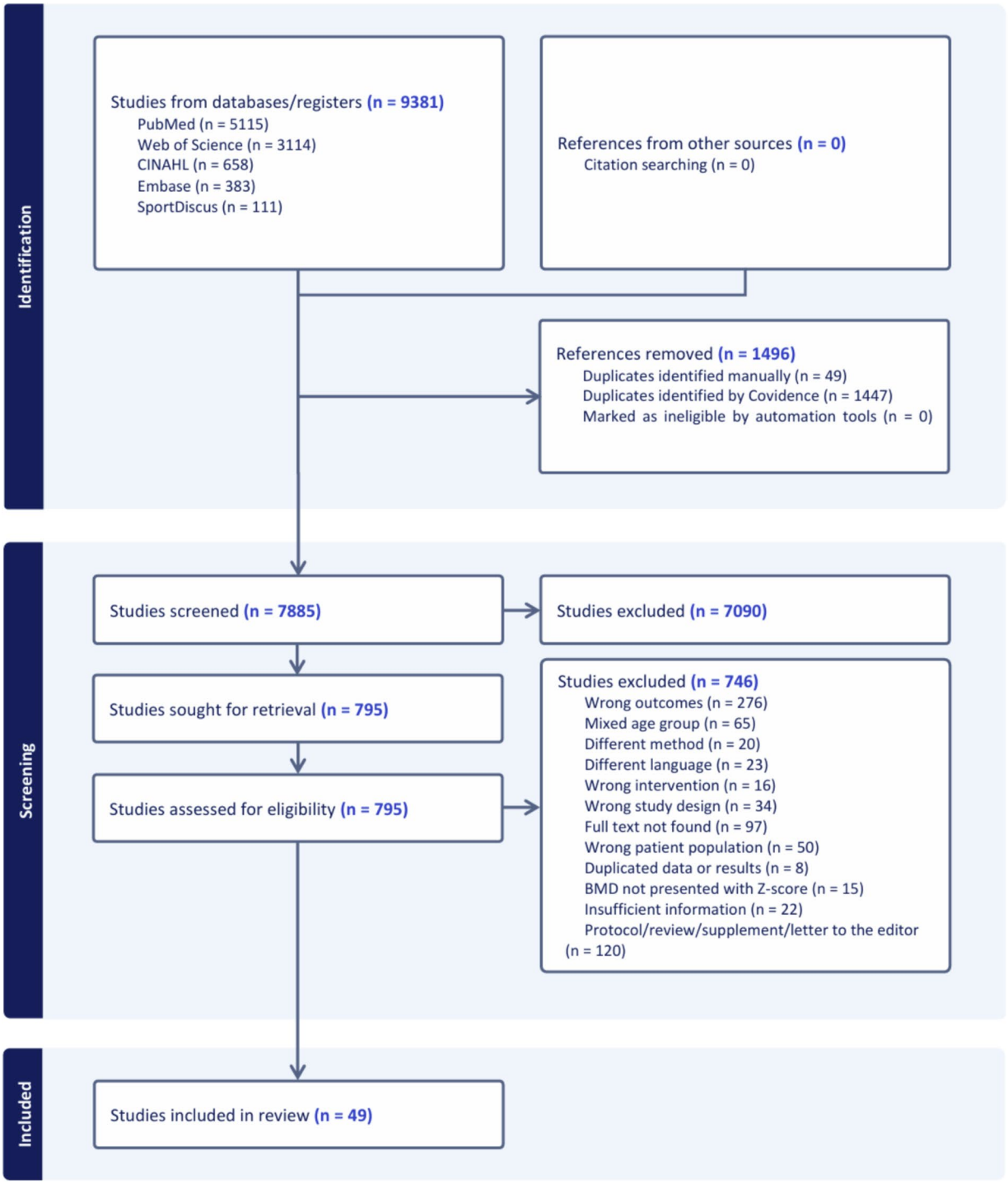

Fig. 1 Flow chart of study selection process

BMD Z-scores in child and adolescent (< 18 years) CCS

Lumbar spine A statistically significant lower lumbar spine BMD Z-score was found (−0.85 SD, 95% CI −1.17 to −0.54; $p < 0.001$; Fig. 2) based on a total of 26 effect sizes across 19 studies. Heterogeneity (I^2) was 48%, and the contour-enhanced funnel plot indicated the presence of publication bias ($\tau = 2.9$; $p = 0.007$; Supplementary Fig. 3). Restricting the analysis to studies that provided means and SDs ($n = 12$) resulted in a greater effect size (−0.99 SD, 95% CI −1.44 to −0.55; $p < 0.001$; Supplementary Fig. 4), but heterogeneity was high (I^2: 60.8%). When restricting the

Table 1 Overall and subgroup analyses of time from diagnosis and region on changes in BMD Z-score in childhood cancer patients undergoing treatment

Multilevel random-effects meta-analysis							
	k	n	*Z*-score Change	95% CI	*P*-value	Q	I^2
BMD Z-score Change							
Overall Effect	14	28	−0.36	−0.62 to −0.11	.010	255.9	73.0%
Time from Diagnosis							
12 months from diagnosis	11	16	−0.37	−0.64 to −0.10	.010	50.1	0.0%
24 months from diagnosis	4	5	−0.28	−1.13 to 0.57	.370	32.0	74.0%
36 months from diagnosis	6	7	−0.23	−0.77 to 0.32	.330	138.3	92.7%
BMD Region							
Lumbar Spine	10	16	−0.17	−0.47 to 0.13	.230	218.4	79.5%
Hip/Femoral Neck	3	4	−0.66	−1.74 to 0.41	.110	17.5	0.0%
Total Body	4	8	−0.79	−0.94 to −0.63	< .001	2.4	0.0%

95% CI, 95% confidence intervals; *BMD*, bone mineral density; I^2, percentage of variation across studies that is due to heterogeneity; *k*, number of clusters; *n*, number of effect sizes; *Q*, Cochran's Q test of heterogeneity

analysis to studies with a score of 5 and above on the NOS ($n=11$), heterogeneity (I^2) was 0% but resulted in a smaller, yet still statistically significant lower BMD (−0.45 SD, 95% CI −0.69 to −0.21; $p<0.001$; Supplementary Fig. 5).

Hip/femoral neck A total of 16 effect sizes across 8 studies were included in the model for hip/femoral neck BMD Z-scores. A statistically significant lower BMD Z-score (−1.03 SD, 95% CI −1.38 to −0.68; $p<0.001$; Fig. 2) was found. Heterogeneity (I^2) was 42.6%, and the contour-enhanced funnel plot did not indicate the presence of publication bias ($\tau=1.1$; $p=0.3$; Supplementary Fig. 6). Restricting the analysis to studies that provided means and SDs ($n=5$) resulted in a greater effect size (−1.18 SD, 95% CI −1.75 to −0.6; $p<0.001$; Supplementary Fig. 7), and heterogeneity (I^2) was 38.4%. Restricting the analysis to studies with a NOS of 5 and above ($n=5$), heterogeneity (I^2) was 0% but resulted in a smaller yet still statistically significant lower BMD (−0.78 SD, 95% CI −1.15 to −0.41; $p<0.001$; Supplementary Fig. 8).

Total body There was no evidence of an effect on total body BMD Z-scores based on 6 effect sizes across 6 studies (−0.09 SD, 95% CI −0.72 to 0.54; $p=0.720$; Supplementary Fig. 9). Heterogeneity (I^2) was 24%, and the contour-enhanced funnel plot did not indicate the presence of publication bias ($\tau=-1.4$; $p=0.247$; Supplementary Fig. 10). Sensitivity analyses were not performed for total body BMD.

BMD Z-scores in adult (> 18 years) CCS

Lumbar spine A statistically significant lower lumbar spine BMD Z-score was found (−0.46 SD, 95% CI −0.67 to −0.26; $p<0.001$; Fig. 3), based on a total of 32 effect sizes across 17 studies. Heterogeneity (I^2) was 24.4%, with the contour-enhanced funnel plot also indicating the absence of publication bias ($\tau=-1.1$; $p=0.264$; Supplementary Fig. 11). Restricting the analysis to studies where means and SDs were not estimated ($n=12$) resulted in a greater effect size (−0.55 SD, 95% CI −0.83 to −0.27; $p<0.001$; Supplementary Fig. 12).

Hip/femoral neck A total of 36 effect sizes across 13 studies were included in the model for hip/femoral neck BMD Z-scores. A statistically significant BMD deficit (−0.36 SD, 95% CI −0.57 to −0.16; $p<0.001$; Fig. 3) was found. Heterogeneity (I^2) was 13.8%, while the contour-enhanced funnel plot indicated the presence of publication bias ($\tau=-2.3$; $p=0.025$; Supplementary Fig. 13). Restricting the analysis to studies where means and SDs were not estimated ($n=8$) resulted in a greater effect size (−0.48 SD, 95% CI −0.79 to −0.17; $p=0.01$; Supplementary Fig. 14).

Total body A total of 16 effect sizes across 9 studies were included in the model for total body BMD Z-scores. There was no evidence of an effect on total body BMD (−0.18 SD, 95% CI −0.56 to 0.2, $p=0.300$; Supplementary Fig. 15). Heterogeneity (I^2) was 43.2%, and contour-enhanced funnel plot indicated the absence of publication bias ($\tau=1.8$; $p=0.091$; Supplementary Fig. 16).

Moderator analysis

There was a significant positive correlation between lumbar spine BMD Z-scores and age at assessment ($p=0.018$), and a significant negative correlation between lumbar spine BMD Z-scores and male sex ($p=0.015$). Time from diagnosis, cohort year, age at diagnosis, and height were not

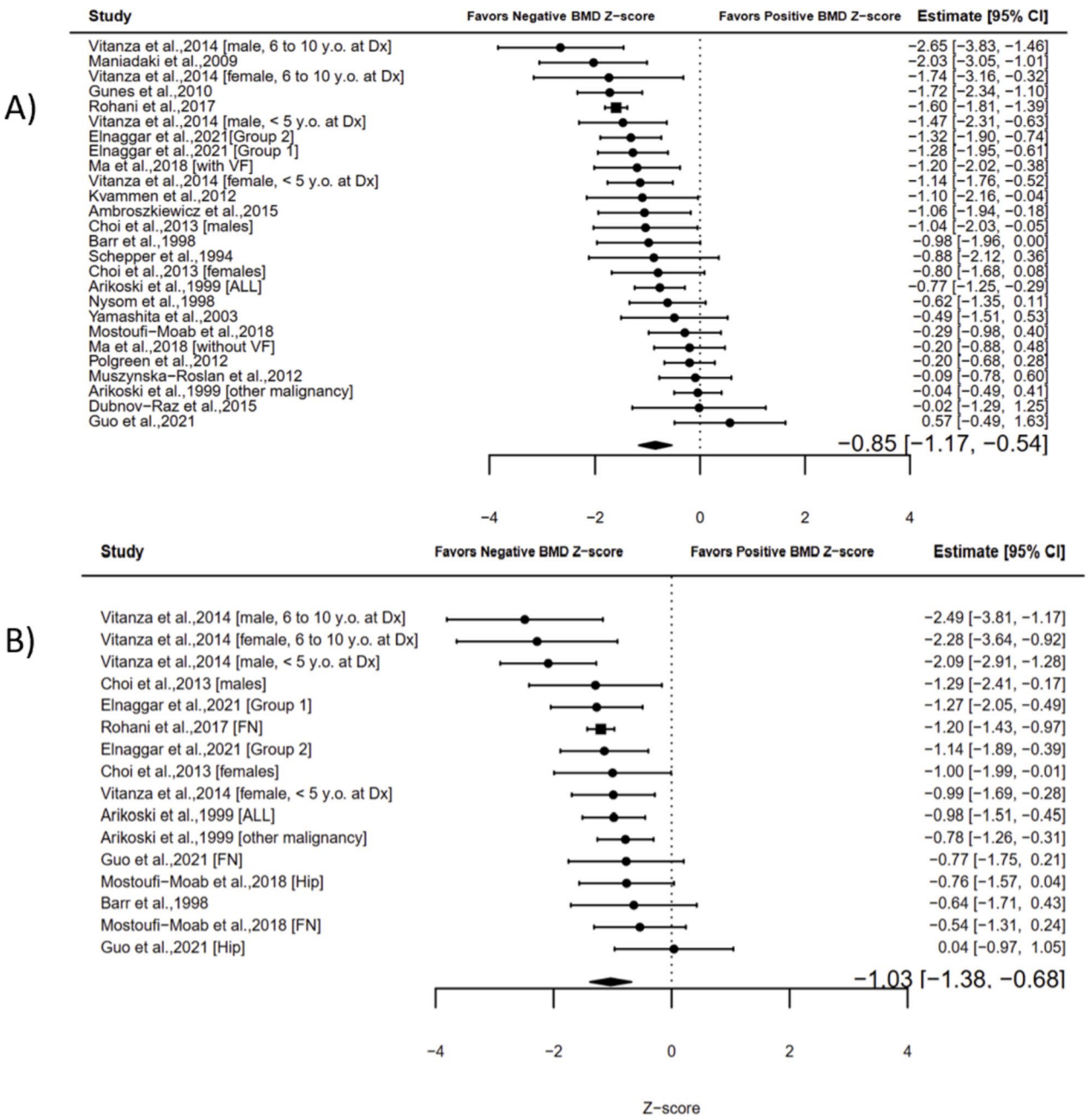

Fig. 2 Forest plots of (**A**) lumbar spine and (**B**) hip/femoral neck BMD Z-scores in child and adolescent survivors (< 18 years old) of childhood cancer

associated with change in this outcome (p = 0.061–0.288; Table 2; Supplementary Figs. 17–22).

At the hip/femoral neck, there was a significant positive correlation between BMD Z-scores and age at assessment (p = 0.004), time from diagnosis ($p = 0.005$), and height ($p = 0.005$), while male sex was negatively correlated with hip/femoral neck BMD Z-scores ($p = 0.027$). Cohort year and age at diagnosis showed no association with this outcome ($p = 0.210$–0.352; Table 2; Supplementary Figs. 23–28). Conversely, at the total body, none of the aforementioned variables were significantly associated with BMD Z-scores ($p = 0.318$–0.981; Table 2; Supplementary Figs. 29–34).

Prevalence of fractures

Six studies (877 patients) were included in the analysis of fracture prevalence among children undergoing cancer treatment. Fracture frequencies ranged from 0/27(0%) to

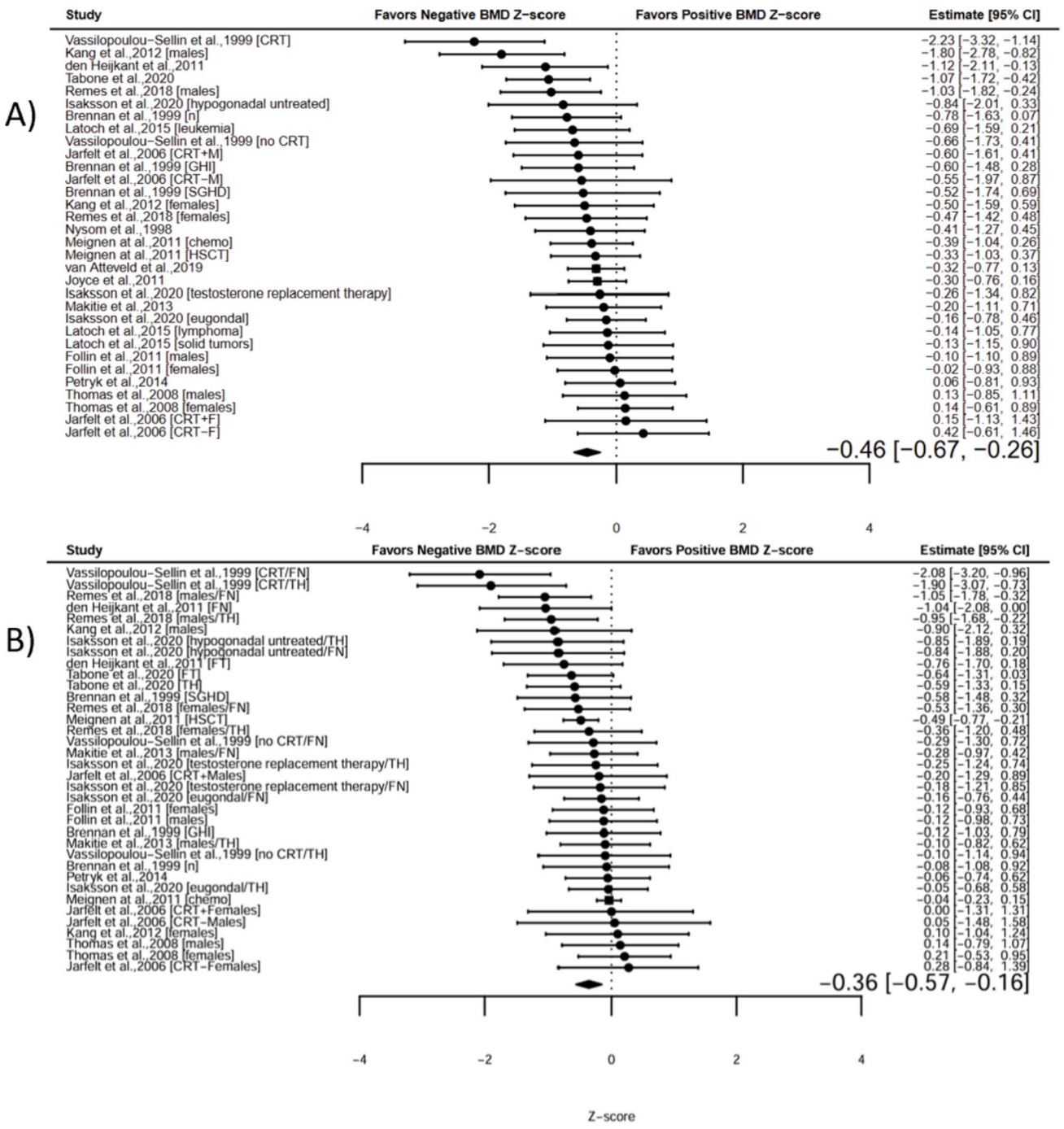

Fig. 3 Forest plots of **A**) lumbar spine and **B**) hip/femoral neck BMD Z-scores in adult survivors (> 18 years old) of childhood cancer

10/41(24%). The pooled fracture prevalence among children undergoing cancer treatment was 13% (95% CI 7 to 19%; Supplementary Fig. 35) with a heterogeneity (I^2) of 82%.

Thirteen studies (919 survivors) were included in the analysis of fracture prevalence in CCS. Fracture frequencies ranged from 0/31(0%) to 40/95(42%). The pooled prevalence of fractures in CCS was 15% (95% CI 9 to 23%; Supplementary Fig. 36) with a heterogeneity (I^2) of 87%.

Discussion

To our knowledge, this is the first meta-analysis to quantify BMD Z-scores in childhood cancer patients and CCS. Our study has three key findings. First, our results indicated a significant decline in BMD Z-scores across different sites in children undergoing cancer treatment, with a more pronounced decrease at the hip/femoral neck compared to the

Table 2 Meta-regression of age at assessment, time from diagnosis, cohort year, age at diagnosis, male sex, and height on lumbar, hip/femoral neck, and total body BMD Z-scores in childhood cancer survivors

Variables		k	n	Univariable model	
Lumbar Spine BMD				β ± SE	*P*-value
	Age at assessment	47	32	0.029 ± 0.011	.018
	Time from Diagnosis	41	27	0.024 ± 0.012	.061
	Cohort Year	34	21	−0.022 ± 0.013	.136
	Age at diagnosis	40	26	−0.063 ± 0.056	.288
	Male Sex	54	34	−0.437 ± 0.139	.015
	Height	25	17	0.020 ± 0.012	.118
Hip/Femoral Neck BMD					
	Age at assessment	42	19	0.035 ± 0.009	.004
	Time from Diagnosis	42	18	0.033 ± 0.009	.005
	Cohort Year	33	12	−0.019 ± 0.019	.352
	Age at diagnosis	40	17	−0.054 ± 0.039	.210
	Male Sex	46	20	−0.394 ± 0.137	.027
	Height	16	8	0.034 ± 0.006	.005
Total Body BMD					
	Age at assessment	19	12	6e-04 ± 0.023	.981
	Time from Diagnosis	14	9	0.001 ± 0.021	.962
	Cohort Year	14	9	−0.011 ± 0.019	.586
	Age at diagnosis	15	10	−0.055 ± 0.074	.530
	Male Sex	21	13	−0.248 ± 0.203	.318
	Height	15	9	0.003 ± 0.008	.741

β, meta-regression coefficient; *BMD*, bone mineral density; *n*, number of studies; *k*, number of effect sizes; *SE*, standard error

lumbar spine. Second, while we noted significantly lower BMD in CCS compared with the non-cancer populations, our meta-regressions indicated older age and female sex were associated with a lower risk for BMD deficits. Third, childhood cancer patients undergoing treatment and CCS are at increased risk of clinically significant fractures.

These results have critical clinical implications. Until recently, the proximal femur was not considered an optimal site for DXA assessment in pediatric populations [5]. However, our results suggest that assessing BMD at weight-bearing sites, particularly in children with limited activity, may be crucial. In a prospective study, each standard deviation decrease in femoral neck BMD was associated with an odds ratio for fracture of 1.8 in healthy boys aged 6.5–8.5 years [72]. This raises the question of whether proximal femur scans could help monitor treatment or disease progression or predict fracture risk.

According to International Society for Clinical Densitometry (ISCD), osteoporosis in pediatric cases is defined as either: (a) the presence of one or more vertebral compression fractures in the absence of local disease or high-energy trauma, or (b) a clinically significant fracture history alongside a BMD Z-score of ≤ -2.0 [73]. In adults younger than 50 years, a Z-score of -2.0 or lower is defined as "below the expected range for age" and alone is not used to diagnose osteoporosis [7], as there are several other powerful predictors of fractures independent of BMD [6]. In our cohort, the BMD Z-score ≤ -2.0 criterion for diagnosing osteoporosis was not met. Nonetheless, fractures were a notable observation, with a pooled fracture prevalence of 15%, comparable with other populations of glucocorticoid-induced osteoporosis in children [74] and adults [75].

The ISCD recognize that a BMD Z-score > -2.0 does not preclude the possibility of a fracture [73]. Our findings, consistent with guidelines from the International Late Effects of Childhood Cancer Guideline Harmonization Group [8], reflect that female sex and a longer time from diagnosis are associated with a lower risk for detecting BMD deficits. Nonetheless, in a Dutch national cohort of 2003 adult CCS, a higher standardized incidence ratio of first fractures was noted in females compared with males (5.35 vs. 3.53, respectively), with the highest being in female CCS aged 30–40 years [2]. This raises the question of whether there are abnormalities in bone microarchitecture contributing to bone fragility. Little is known about how anticancer treatments affect the structural and material properties of bones [76]. It is also noteworthy that while information on the sex of the participants in the included studies was obtained primarily through clinical/physical examinations or medical records, in some studies, the method for assigning sex/gender was less clear.

Finally, we did not find that BMD was moderated by cohort year and age at diagnosis. Indeed, despite advances in treating childhood cancers, treatment approaches vary across different cancer types and risk groups. For example, the higher the risk a child with acute lymphoblastic leukemia is determined to have, the more intense the treatment. Age at diagnosis is one prognostic factor included in risk stratification schemes [77]. While there were no differences in BMD based on age at diagnosis, it is crucial to note that our findings were derived from population mean values. Accordingly, future research should prioritise evaluating individual patient data to gain deeper insights into the impacts of specific treatment strategies/doses and test the effectiveness of adjunct treatments such as targeted exercise and diet therapy to prevent bone loss in childhood cancer patients and survivors.

Strengths, Limitations and Risk of Bias

The strengths of this review include: (a) compiling 49 studies with 4547 childhood cancer patients and survivors; (b) using a three-level mixed-effects meta-analysis to account for the nested structure of the effect sizes calculated from the included studies; and (c) conducting subgroup, sensitivity, and meta-regression analyses for a range of non-modifiable factors (i.e., age at diagnosis, sex, age at assessment, time from diagnosis, cohort year, height) and methodological characteristics (i.e., study quality, skeletal site assessed).

Nonetheless, our meta-analysis has limitations. First, it has been previously shown that a single absolute lumbar spine BMD value in CCS under age 18 can generate markedly different BMD Z-scores, depending on the pediatric reference used [78]. While this is unlikely to have affected our prospective analyses, as we analysed within group BMD Z-score changes, it may have partly contributed to the relatively higher heterogeneity in BMD Z-scores in CCS below age 18. This was one of the reasons for limiting the review to original studies that exclusively included CCS under or above 18 years. To investigate sources of heterogeneity, we performed sensitivity analyses. We observed that excluding studies with the lowest NOS score (4 points) reduced heterogeneity to nil. The excluded studies scored fewer points due to using a different DXA manufacturer in the CCS vs. the control groups (thus a different technology) or because results were not compared with community (local) population BMD scores. Second, areal BMD by DXA is subject to size artifacts. We performed meta-regressions for height and noted an association with hip/femoral neck BMD Z-scores, with shorter individuals showing lower BMD values. While adjusting BMD Z-scores for growth has been an ongoing focus for pediatric bone experts [79], these recommendations are rarely implicated and incorporated into practice. Finally, our cohort of adult long-term CCS had a mean age of 27, meaning they have yet to reach an age at which the underlying population risk of fracture increases substantially. Little is known about the BMD status of aging CCS [76].

Conclusion

Our findings demonstrate a decline in BMD in children undergoing cancer treatments, which persists through survivorship and into adulthood. Considering the growing population of adult CCS, these findings are important. Efforts should be made to increase awareness of the adverse effects of cancer treatments on BMD. Additionally, future research should evaluate the effectiveness of adjunct treatments such as targeted exercise and diet therapy to prevent bone loss in childhood cancer patients and survivors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07458-5.

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Data availability The data that support the findings of this study are available from the corresponding author upon request.

Declarations

Conflict of interest Anna Maria Markarian, Robert U. Newton, Dennis R. Taaffe, Daniel A. Galvão, Jodie Cochrane Wilkie, Carolyn McIntyre, Francesco Bettariga, and Hao Luo declare that they have no conflicts of interest relevant to the content of this study.

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